General

Guideline Title

National Institutes of Health State-of-the-Science Conference statement: role of active surveillance in the management of men with localized prostate cancer.

Bibliographic Source(s)

Ganz PA, Barry JM, Burke W, Col NF, Corso PS, Dodson E, Hammond ME, Kogan BA, Lynch CF, Newcomer L, Seifter EJ, Tooze JA, Viswanath K, Wessells H. National Institutes of Health State-of-the-Science Conference statement: role of active surveillance in the management of men with localized prostate cancer. NIH Consens State Sci Statements. 2011 Dec 5-7;28(1):1-27.

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Prostate cancer screening with prostate-specific antigen (PSA) testing has identified many men with low-risk disease. Because of the very favorable prognosis of low-risk prostate cancer, strong consideration should be given to modifying the anxiety-provoking term "cancer" for this condition. Treatment of low-risk prostate cancer patients with radical prostatectomy or radiation therapy leads to side effects such as impotence and incontinence in a substantial number. Active surveillance has emerged as a viable option that should be offered to patients with low-risk prostate cancer. More than 100,000 men a year diagnosed with prostate cancer in the United States are candidates for this approach. However, there are many unanswered questions about active surveillance strategies and prostate cancer that require further research and clarification. These include:

- Improvements in the accuracy and consistency of pathologic diagnosis of prostate cancer
- Consensus on which men are the most appropriate candidates for active surveillance
- The optimal protocol for active surveillance and the potential for individualizing the approach based on clinical and patient factors
- Optimal ways to communicate the option of active surveillance to patients
- Methods to assist patient decision-making
- Reasons for acceptance or rejection of active surveillance as a treatment strategy
- Short- and long-term outcomes of active surveillance

Well-designed studies to address these questions and others raised in this statement represent an important health research priority. Qualitative, observational, and interventional research designs are needed. Due to the paucity of evidence about this important public health problem, all patients being considered for active surveillance should be offered participation in multicenter research studies that incorporate community settings

and partners.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Localized prostate cancer

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Oncology

Pathology

Urology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To provide healthcare providers, patients, and the general public with a responsible assessment of currently available data on the use of active

surveillance and other observational management strategies for low-grade, localized prostate cancer

Target Population

Men with localized prostate cancer

Interventions and Practices Considered

Active surveillance in the management of localized prostate cancer

Major Outcomes Considered

- Incidence of prostate cancer
- Survival rates
- Prostate-specific and all-cause mortality
- Morbidity of primary treatment
- Incidence of metastatic disease
- Disease-specific quality of life
- Short- and long-term costs

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic review of the literature was prepared by the Tufts Evidence-based Practice Center (EPC), Tufts Medical Center, Boston, MA for the Agency for Healthcare Research and Quality (AHRQ) for use by the National Institutes of Health (NIH) (see the "Availability of Companion Documents" field).

Literature Searches, Eligibility Criteria, and Screening

Multiple literature searches were performed in MEDLINE from inception to August 2011. The EPC staff searched for recent systematic reviews, and subsequently conducted separate but overlapping searches for each of the first four Key Questions. They used search terms related to prostate cancer, active surveillance, watchful waiting, expectant management, and other related management strategies. They also searched for studies of specific databases, including SEER (Surveillance Epidemiology and End Results) and CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor). For Key Question 4, the EPC staff relied on previous systematic reviews on prostate cancer conducted for the AHRQ EPC program. Searches were supplemented with studies recommended to EPC by the Technical Expert Panel, reference lists of eligible primary studies and relevant review articles, and targeted searches for economic evaluations. The EPC staff did not include unpublished data.

Below are the study eligibility criteria used for the first four Key Questions (no specific literature search was performed for Key Question 5):

Key Question 1. Studies of large U.S.-based databases of patients with prostate cancer with time-trend data (reporting changes over a range of years) between 1980 and 2011. Studies must have had a sample size of at least 1000 patients. The latest version of the American Cancer Society Cancer Statistics report, a recent SEER Survival Monograph, and data available on the SEER Web site were also reviewed.

Key Question 2. Studies of any design that reported protocols and management strategies for patients receiving observational management (i.e., no

immediate curative treatment). The EPC staff included both studies where the goal of observation was to identify disease progression indicative of the need for curative treatments, and studies where the goal of observation was to determine the need for palliative treatments.

Key Question 3. Three types of studies were included. Firstly, the EPC included studies that used quantitative methods to analyze databases or cohorts of patients to elucidate predictors of the offer or acceptance of or adherence to observational management strategies (including active surveillance [AS] and watchful waiting [WW]). Studies that analyzed androgen deprivation therapy (ADT) together with observational management strategies were excluded. The EPC required multivariable analyses adjusting for a minimum of age and tumor stage (if the analysis was not limited to localized cancer) or using a propensity score. Secondly, the EPC included studies using qualitative research methods (e.g., focus groups or surveys) to obtain information on factors that affect the offer or acceptance of or adherence to AS or WW. Eligible studies must have used a predefined approach to collect information. Thirdly, the EPC staff also searched for experimental studies evaluating the effect of tools, such as decision aids, on the offer or acceptance of or adherence to AS (however, no such studies were found).

Key Question 4. Randomized and nonrandomized, prospective or retrospective longitudinal comparative studies performed in a multicenter setting were included. Nonrandomized studies must have used multivariable or other methods to adjust for possible confounding, specifically for age and tumor stage, to warrant inclusion. The population of interest was men with clinically localized prostate cancer (T1-T2), without known lymph nodes (N0-X) or metastases (M0-X). No more than 20 percent of the study sample could exhibit more advanced disease. Studies had to compare observational management strategies (without ADT) to active treatment, including radical prostatectomy [RP], external beam radiation therapy (EBRT), or brachytherapy (BT), all with or without ADT. However, ADT monotherapy was not considered an active treatment. Outcomes of interest included: prostate cancer mortality, all-cause mortality, morbidity of primary treatment, metastatic disease, quality of life, and costs.

All five EPC team members participated in screening and selecting studies. An iterative screening process was used for training and to ensure consistency in application of eligibility criteria. Abstracts were screened once. A very low threshold was used to mark a study as of possible interest. During full-text screening, equivocal articles were screened by at least two team members.

Refer to Appendix A of the Evidence Review (see the "Availability of Companion Documents" field) for additional information on search strategies.

Number of Source Documents

A total of 195 papers and 4 evidence/economic reports met criteria and are included in the review.

Key Question (KQ) 1: 79 primary studies, 1 systematic review

KQ 2: 35 unique cohorts (in 56 publications)

KQ 3: 41 primary studies, 1 systematic review

KQ 4: 2 randomized controlled trials (RCTs, 4 publications), 16 cohort studies, 2 Evidence-based Practice Center (EPC) reports, 2 Institute for Clinical and Economic Review (ICER) reports, 2 additional cost-modeling studies

Note: The numbers of studies for each Key Question do not sum to the total number of included studies because some studies addressed multiple Key Questions.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Studies as Described in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide

A (good). Quality A studies have the least likelihood of bias, and their results are considered most valid. They generally possess the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; clear reporting of dropouts and a dropout rate less than 20 percent; and no obvious bias. Only prospective studies may receive a grade of A.

B (fair/moderate). Quality B studies are susceptible to some bias, but not sufficiently to invalidate results. They do not meet all the criteria in category A due to some deficiencies, but none likely to introduce major bias. Quality B studies may be missing information, making it difficult to

assess limitations and potential problems.

C (poor). Quality C studies have been adjudged to carry a substantial risk of bias that may invalidate the reported findings. These studies have serious errors in design, analysis, or reporting and contain discrepancies in reporting or have large amounts of missing information.

Strength of Evidence Grades (as per the AHRQ methods guide)

High. There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change confidence in the estimate of effect. No important scientific disagreement exists across studies. At least two quality A studies are required for this rating. In addition, there must be evidence regarding objective clinical outcomes.

Moderate. There is moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of effect and may change the estimate. Little disagreement exists across studies. Moderately rated bodies of evidence contain fewer than two quality A studies or such studies are inconsistent or lack long-term outcomes of relevant populations.

Low. There is low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. Underlying studies may report conflicting results. Low rated bodies of evidence could contain either quality B or C studies.

Insufficient. Evidence is either unavailable or does not permit a conclusion. There are sparse or no data. In general, when only one study has been published, the evidence was considered insufficient, unless the study was particularly large, robust, and of good quality.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic review of the literature was prepared by the Tufts Evidence-based Practice Center (EPC), Tufts Medical Center for the Agency for Healthcare Research and Quality (AHRQ) for use by the National Institutes of Health (NIH) (see the "Availability of Companion Documents" field).

Data Extraction

Bibliographic data, eligibility criteria, enrollment years, study duration, and sample size were extracted for all studies. For Key Question 1, the EPC staff extracted data that allowed reconstruction of trends over time in incidence and mortality, as well as patient-, tumor-, and system-level characteristics of interest. The data were extracted into tables of 5-year bins (e.g., 1980-84, 1985-89) from 1980 to 2010. EPC staff extracted reported statistical data regarding changes over time in factors of interest. For Key Question 2, data were extracted on patient- and tumor-level characteristics used as eligibility criteria, follow-up or monitoring parameters, and specific triggers for definitive treatment. EPC staff also extracted definitions of disease progression. For quantitative studies (multivariable models) related to Key Question 3, the definition of the observational strategy, factors of interest, and effect sizes were extracted. For qualitative studies (surveys) related to Key Question 3, EPC staff extracted the specific survey approach used, the definition of the observational strategy addressed, the qualitative summary of the key study findings, and information to assess the study validity (e.g., survey response rate, survey validation). For Key Question 4, details about the study population (including eligibility criteria and baseline characteristics), specific interventions compared, outcome definitions, study design, and effect sizes of outcomes of interest were extracted.

Quality Assessment

EPC staff formally assessed methodological quality only for studies included for Key Question 4. Studies were graded using standard AHRQ EPC methodology with a three-level grading system (A, B, or C) (see the "Rating Scheme for the Strength of the Evidence" field). For randomized controlled trials (RCTs), they primarily considered the methods used for randomization, allocation concealment, and blinding, as well as the use of intention-to-treat analysis, the report of dropout rate, and the extent to which valid primary outcomes were described and clearly reported. Only RCTs and prospective comparative studies could receive an A grade. Retrospective studies could be graded either B or C. For all studies, EPC staff used the following in their assessment (as applicable): the report of eligibility criteria, the similarity of the comparative groups in terms of baseline characteristics and prognostic factors, the report of intention-to-treat analysis, important differential loss to follow-up between the

comparative groups or overall high loss to follow-up, and the validity and adequacy of the description of outcomes and results. Quality A studies are those judged to have the least likelihood of bias and are considered the most internally valid. Quality C studies have a substantial risk of bias and may not be valid. Quality assessment was performed by the team member responsible for primary data extraction. The quality grade was confirmed by at least one other team member.

Data Synthesis

All included study data were tabulated into summary tables (refer to Appendix C of the Evidence Report [see the "Availability of Companion Documents" field]) that succinctly describe the important study characteristics and their findings. Time-trend data for Key Question 1 were graphed over the interval of interest (1980–2010). Although the EPC considered generating forest plots for comparative effectiveness data for Key Question 4, the data were inadequate for forest plots to be informative (i.e., there were generally only one or two studies addressing a specific question).

Grading the Body of Evidence

The EPC graded the body of evidence only for the comparative effectiveness review portion of the systematic review (i.e., Key Question 4). They used standard AHRQ EPC methodology (see the "Rating Scheme for the Strength of the Evidence" field). They assessed the risk of bias of the studies based on their study design and methodological quality, the consistency of data across studies, the applicability of the studies to the U.S. population of men with localized prostate cancer, potential problems with measurement of outcomes in studies, and the precision and sparseness of data. The strength of evidence was rated on a four-level scale: High, Moderate, Low, and Insufficient. Ratings were assigned based on the level of confidence that the evidence reflected the true effect for the major comparisons of interest.

Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

National Institutes of Health (NIH) Consensus and State-of-the-Science Statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and the morning of the third.

The National Cancer Institute, the Centers for Disease Control and Prevention, and the Office of Medical Applications of Research in the NIH Office of Disease Prevention convened a State-of-the-Science Conference on December 5–7, 2011, to assess the available scientific evidence.

Participants included a non-U.S. Department of Health and Human Services, nonadvocate 14-member panel representing the fields of cancer prevention and control, urology, pathology, epidemiology, genetics, transplantation, bioethics, economics, health services research, shared decision-making, health communication, and community engagement. In addition, 22 experts from pertinent fields presented data to the panel and conference audience.

The panel was asked to address the following key questions:

1. How have the patient population and the natural history of prostate cancer diagnosed in the United States changed in the last 30 years?
2. How are active surveillance and other observational strategies defined?
3. What factors affect the offer of, acceptance of, and adherence to active surveillance.
4. What are the patient-experienced comparative short- and long-term health outcomes of active surveillance versus immediate treatment with curative intent for localized prostate cancer?
5. What are the research needs regarding active surveillance (or watchful waiting) in localized prostate cancer?

During the first 2 days of the conference, experts presented information on each of the key questions. After weighing the scientific evidence, including the data presented by the speakers, input from the attendees, and a formal evidence report commissioned through the Agency for Healthcare Research and Quality, an independent panel prepared and presented a draft of this State-of-the-Science Statement addressing the conference questions.

The draft statement was presented on the final day of the conference and circulated to the audience for comment. The panel released a revised

statement later that day at http://consensus.nih.gov .

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Published cost-effectiveness analyses were reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The draft statement was presented on the final day of the NIH State-of-the-Science Conference: Role of active surveillance in men with localized prostate cancer and circulated to the audience for comment. The panel released a revised statement later that day at http://consensus.nih.gov .

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is not specifically stated for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Better understanding the currently available data on the role of active surveillance in the management of men with localized prostate cancer
- Enabling patients receiving active surveillance to avoid or delay the side effects of treatment

Potential Harms

There are side effects associated with any treatment strategy for prostate cancer:

- Radical prostatectomy causes sexual dysfunction and urinary incontinence in a substantial proportion of patients. In addition, there is 30-day mortality of one-half percent.
- Radiation therapy often causes bowel, sexual, and urinary dysfunction.
- Active surveillance complications include biopsy-related infections, pain, and anxiety.

Qualifying Statements

Qualifying Statements

Qualifying Statements

- The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research, and that the information provided is not a substitute for professional medical care or advice.
- This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health (NIH) or the Federal Government.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Ganz PA, Barry JM, Burke W, Col NF, Corso PS, Dodson E, Hammond ME, Kogan BA, Lynch CF, Newcomer L, Seifter EJ, Tooze JA, Viswanath K, Wessells H. National Institutes of Health State-of-the-Science Conference statement: role of active surveillance in the management of men with localized prostate cancer. NIH Consens State Sci Statements. 2011 Dec 5-7;28(1):1-27.

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Dec

Guideline Developer(s)

National Institutes of Health Consensus Development Conference - Independent Expert Panel

Source(s) of Funding

United States Government

Guideline Committee

National Institutes of Health (NIH) State-of-the-Science Panel

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Financial Disclosures/Conflicts of Interest

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on National Institutes of Health (NIH) Consensus and State-of-the-Science Panels are reviewed prior to selection to ensure that they are not proponents of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

For more information about conference procedures, please see http://consensus.nih.gov/aboutcdp.htm.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institutes of Health (NIH) Consensus Development Conference Program Web site .

Print copies: Available from the NIH Consensus Development Program Information Center, PO Box 2577, Kensington, MD 20891; Toll free phone (in U.S.), 1-888-NIH-CONSENSUS (1-888-644-2667); autofax (in U.S.), 1-888-NIH-CONSENSUS (1-888-644-2667); e-mail: consensus_statements@mail.nih.gov.

Availability of Companion Documents

The following are available:

- Ip S, Dahabreh IJ, Chung M, Yu WW, Balk EM, Iovin RC, Mathew P, Luongo T, Dvorak T, Lau J. An evidence review of active surveillance in men with localized prostate cancer. Evidence Report/Technology Assessment No. 204. (Prepared by Tufts Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) AHRQ Publication No. 12-E003-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2011. Available from the Agency for Healthcare Research and Quality (AHRQ) Web site .
- Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J, Ip S. Active surveillance in men with localized prostate cancer: a systematic review. Ann Intern Med. 2012 Apr 17;156(8):582-590. Available from the Annals of Internal Medicine Web site .
- The NIH State-of-the-Science Conference: Role of active surveillance in the management of men with localized prostate cancer. Webcast. December 5–7, 2011. Available from the NIH Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 2, 2012.

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